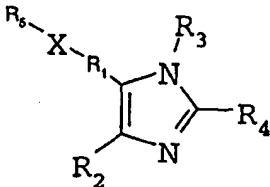




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(54) Title: ANTI-INFLAMMATORY 4-PHENYL-5-PYRIMIDINYL-IMIDAZOLES <div style="text-align: center;">  (I) </div> (57) Abstract <p>Novel 4- phenyl- 5-(2- aryl-X)- 4-pyrimidinyl-, 4- phenyl-5- (2-cycloalkyl- X)-4-pyrimidinyl-, 4- phenyl-5- (-aralkyl-X)-4-pyrimidinyl- or 4-phenyl- 5-(2-cycloalkylalkyl- X)-4-pyrimidinyl- imidazoles, in which the 5- pyrimidinyl substituent is aryl, cycloalkyl, aralkyl or cycloalkylalkyl substituted directly via a heteroatom X selected from N, O or S, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof are provided, in particular compounds of formula (I), wherein the symbols are as defined, which are MAP kinase inhibitors, useful pharmaceutically for treating TNFα and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis.</p>		

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ANTI-INFLAMMATORY 4-PHENYL-5-PYRIMIDINYL-IMIDAZOLES

This invention relates to 4-phenyl-5-[(2-substituted)-4-pyrimidinyl]-1-H-imidazoles which are the tautomeres of 5-phenyl-4-[(2-substituted)-4-pyrimidinyl]-1-H-imidazoles and to their use for treating TNF α and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis. Both tautomers represent the same structure; their nomenclature may be used interchangeably.

Accordingly the present invention provides novel 4-phenyl-5-[(2-aryl-X)-4-pyrimidinyl]-, 4-phenyl-5-[(2-cycloalkyl-X)-4-pyrimidinyl]-, 4-phenyl-5-(2-aralkyl-X)-4-pyrimidinyl- or 4-phenyl-5-[(2-cycloalkylalkyl-X)-4-pyrimidinyl]-imidazoles, in which X is a heteroatom selected from N, O or S, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

The 5-pyrimidinyl substituent is aryl-, cycloalkyl-, aralkyl- or cycloalkylalkyl-substituted directly via a heteroatom selected from N, O or S, i.e. the aryl, cycloalkyl, aralkyl or cycloalkylalkyl substituent and the pyrimidinyl ring are linked by a single atom which is N, O or S. Preferably the heteroatom is optionally substituted N, more preferably -NH-.

The aryl or aralkyl substituent may comprise a carboaryl substituent or a heteroaryl substituent; for instance, phenyl, benzyl, phenylethyl, 4-pyridylmethyl, naphthyl (e.g. naphth-1-yl or naphth-2-yl), pyridyl (e.g. 4-pyridyl), pyrimidinyl, quinazolinyl (e.g. quinazolin-4-yl), quinolinyl, isoquinolinyl, imidazolyl (e.g. 2- or 3-imidazolyl) or benzamidazolyl (e.g. 2-benzamidazolyl). The cycloalkyl or cycloalkylalkyl substituent may comprise a C₃ to C₁₂ cycloalkyl ring, e.g. a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl ring. The aryl, cycloalkyl, aralkyl and cycloalkylalkyl substituents may be optionally substituted, e.g. by up to 3 substituents selected from alkyl, halogen, halo-substituted-alkyl, hydroxy, alkoxy, alkylthio, optionally substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom (e.g. O, S or N). Preferably the aryl or aralkyl substituent on the 5-pyrimidinyl substituent is benzyl, phenylethyl, 4-pyridylmethyl or phenyl, optionally substituted, preferably in the meta and/or para positions, by halogen, C₁₋₁₀alkyl, C₁-

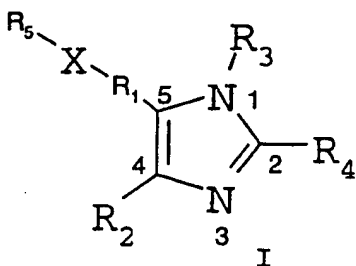
alkoxy, hydroxy, halo-substituted C_{1-10} alkyl (e.g. trifluoromethyl), or optionally substituted amino.

The 4-phenyl substituent may be unsubstituted, though is preferably substituted by one or more substituents, each of which may be independently selected from halo, cyano, amido, thioamido, carboxylate (including thiocarboxylate and esters of both of these), optionally substituted C_{0-1} alkyl optionally substituted carbonyl or thiocarbonyl (i.e. both aldehyde and ketone), alkoxy or thioalkoxy, optionally substituted alkyl, optionally substituted oxycarbonyl or aminocarbonyl (including thio analogues thereof), (optionally substituted)-amino or -aminomethyl, optionally substituted alkylamino-carbonyl or -thiocarbonyl, optionally substituted amino-sulphinyl or -sulphonyl optionally substituted by amino. Preferably the 4-phenyl has up to 3 substituents and preferably these are halo or halo-containing substituents, e.g. the 4-phenyl substituent is 2, 4, 5 trihalo-substituted phen-1-yl or especially 4-halo-, 3-trifluoromethyl, 3-chloro, or 3,4-difluoro substituted.

The C-2 and N1 atoms of the of the imidazole ring may also be substituted, conveniently by substituents such as those described at equivalent positions in WO 95/03297, WO 97/25048, WO 97/12876 or WO 99/01499. The numbering of the atoms of the imidazole ring is shown below in Figure I.

Above and elsewhere in the present description the terms halo or halogen denote I, Br, Cl or F, preferably F.

In particular embodiments the invention provides a compound of formula I



wherein

R₁ is pyrimidinyl;

X is -NR₆-Y-, -O- or -S-,

where R₆ is H, C₁₋₄alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkylC₁₋₃alkyl, C₆₋₁₈aryl, C₃₋₁₈heteroaryl, C₇₋₁₉aralkyl or C₄₋₁₉heteroaralkyl, and -Y- is C₁₋₄alkylene or a direct bond ;

R₂ is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF₃,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C₁₋₄alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C₁₋₄alkyl C₁₋₄alkylcarbonyl or C₁₋₄alkylthiocarbonyl substituted,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C₁₋₁₀alkoxy, C₂₋₁₀alkenoxy, C₂₋₁₀alkynoxy, C₃₋₇cycloalkoxy, C₅₋₇cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester, optionally mono- or di-C₁₋₄alkyl-substituted-C₀₋₁alkyl optionally C₁₋₄alkyl- or C₃₋₅cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted-C₁₋₄alkoxy, C₂₋₄alkenoxy, C₂₋₄alkynoxy, C₃₋₅cycloalkoxy or C₃₋₅cyclothioalkoxy,

optionally halo substituted C₁₋₄ alkyl,

oxycarbonyl or optionally N-C₁₋₄alkyl-substituted aminocarbonyl both of which are optionally C₁₋₄alkyl or C₃₋₅cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di-C₁₋₄alkyl-substituted-C₀₋₁alkylamine which is optionally mono-or di-N-C₁₋₄ alkyl substituted,

optionally mono- or di-C₁₋₄alkyl-substituted-C₀₋₁alkyl optionally N-C₁₋₄alkyl-substituted amino-carbonyl or -thiocarbonyl,

optionally N-C₁₋₄alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C₁₋₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁₋₄alkyl C₁₋₄alkylcarbonyl or C₁₋₄alkylthiocarbonyl substituted, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C₁₋₄alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl,

optionally mono- or di-N-C₁₋₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁₋₄alkyl C₁₋₄alkylcarbonyl or C₁₋₄alkylthiocarbonyl substituted;

R₃ is hydrogen,

heterocyclyl,

heterocyclylC₁₋₁₀alkyl,

optionally halo substituted C₁₋₁₀alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₁₀alkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀alkyl, heteroaryl, or heteroarylC₁₋₁₀alkyl,

optionally mono-or di-C₁₋₄alkyl-substitutedC₀₋₁₀alkyl-oxycarbonyl or -oxythiocarbonyl optionally substituted by C₁₋₁₀alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl, aryl, arylC₁₋₁₀alkyl, heteroaryl, heteroarylC₁₋₁₀alkyl, or

optionally mono-or di-C₁₋₄alkyl-substitutedC₁₋₁₀alkyl

-cyano,

-nitro,

-hydroxy, -C₁₋₁₀alkoxy, -C₃₋₇cycloalkoxy, -heterocycloxy, -heterocyclylC₁₋₁₀alkoxy, -aryloxy, -arylC₁₋₁₀alkoxy, -heteroaryloxy, -heteroarylC₁₋₁₀alkoxy (and thio oxy analogues thereof),

optionally substituted amino, carboxylate, thiocarboxylate, carbonyl or thiocarbonyl, sulphinyl or sulphonyl;

R₄ is H, or C₁₋₁₀alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₈heterocycloalkyl, C₆₋₁₈aryl, or C₃₋₁₈heteroaryl all optionally substituted by up to 4 substituents separately selected from alkyl, halogen, halo-substituted-alkyl, hydroxy, alkoxy, alkylthio, or optionally substituted amino;

R₅ is C₆-C₁₈aryl, C₃-C₁₈heteroaryl, or C₃-C₁₂cycloalkyl optionally substituted by up to 3 substituents separately selected from alkyl, halogen, halo-substituted-alkyl, hydroxy, alkoxy, alkylthio, optionally substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

R₁ is preferably 4-pyrimidinyl.

When R₄ is alkyl it is C₁-C₁₀alkyl, preferably C₁-C₆alkyl, optionally substituted, preferably with one or two substituents separately selected from hydroxy, C₁-₆alkoxy or amino.

When R₄ is aryl or heteroaryl either of which is optionally substituted by up to 4 substituents, R₄ may comprise one of the customary aryl or heteroaryl substituents in the art and may be substituted as is customary in the art; for instance as defined for the substituent R₃ of WO 93/03297.

When R₄ is cycloalkyl it is preferably C₃-C₈, especially C₅-C₆cycloalkyl (e.g. cyclohexyl), optionally substituted, preferably with up to 2 substituents separately selected from alkyl, halogen, hydroxy, alkoxy, or amino.

When R₄ is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, optionally substituted, e.g. by up to 2 substituents, selected from halogen, hydroxy, alkoxy, or amino.

When R₅ is aryl it is preferably phenyl. When R₅ is cycloalkyl, it is preferably C₃-C₇cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. R₅ may be unsubstituted or substituted, preferably mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen, C₁-₁₀alkyl, halo-substituted C₁-₁₀alkyl, C₁-₁₀alkoxy, hydroxy or -NR₇R₈, where R₇ and R₈ are independently H, C₁-₆alkyl, C₆-₁₀aryl, C₆-₁₀heteroaryl, C₇-₁₁aralkyl or C₇-₁₁heteroaralkyl.

When -Y- is C₁-C₄ alkylene, it is preferably C₁-C₂ alkylene, and is optionally substituted, e.g. by C₁-C₄alkyl (e.g. methyl), halogen, hydroxy, alkoxy, or amino.

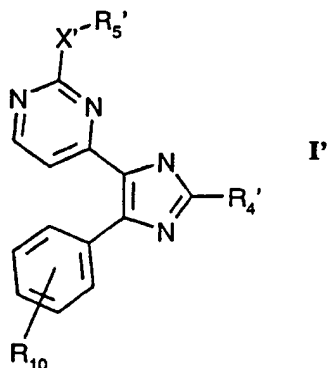
Preferably R_2 is phenyl substituted, preferably mono-substituted, by halogen, e.g. 4-fluorophen-1-yl, or 3- CF_3 , 3-Cl, or 3,4-difluoro substituted.

Preferably R_3 is H.

Preferably R_4 is H or C_{1-6} lower alkyl, 1-hydroxy C_{1-10} alkyl, 1- C_{1-6} alkoxy C_{1-10} alkyl, 1-amino C_{1-10} alkyl, 1-hydroxy C_{3-10} cycloalkyl, 1- C_{1-6} alkoxy C_{3-10} cycloalkyl, 1-amino C_{3-10} cycloalkyl, 1-hydroxy C_{3-18} heterocycloalkyl, or 1- C_{1-6} alkoxy C_{3-18} heterocycloalkyl.

Preferably X is -NH-Y'-, -O- or -S-, where Y' is - CH_2 -, - CH_2-CH_2 -, -CH(CH_3)- or a direct bond

Thus in preferred embodiments the invention provides a compound of formula I'



wherein

R_5' is phenyl or C_3 - C_7 cycloalkyl each of which is optionally mono-substituted by halogen, C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, trihalomethyl or - NR_7R_8 , where R_7 and R_8 are independently H, C_{1-6} alkyl, C_{6-10} aryl, C_{6-10} heteroaryl, C_{7-11} aralkyl or C_{7-11} heteroaralkyl;

R_{10} is halogen, cyano, amido, thioamido, amino or C_{1-6} alkyl;

R_4' is H, C_{1-6} alkyl, 1-hydroxy C_{1-10} alkyl, 1- C_{1-6} alkoxy C_{1-10} alkyl, 1-amino C_{1-10} alkyl, 1-hydroxy C_{3-10} cycloalkyl, 1- C_{1-6} alkoxy C_{3-10} cycloalkyl, 1-amino C_{3-10} cycloalkyl, 1-hydroxy C_{3-18} heterocycloalkyl, or 1- C_{1-6} alkoxy C_{3-18} heterocycloalkyl, and

X' is -NH-Y'-, -O- or -S-, where Y' is - CH_2 -, - CH_2-CH_2 -, -CH(CH_3)- or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

In the present description the terms such as "C₃₋₁₈heteroaryl, C₄₋₁₉heteroaralkyl and C₃₋₁₈heterocycloalkyl" denote heteroaryl, heteroaralkyl or heterocycloalkyl substituents comprising at least 3 ring atoms, at least one of which is a hetero atom, e.g. N, O or S, and which in the case of C₄₋₁₉heteroaralkyl groups are attached via an alkylene moiety comprising at least 1 carbon atom.

Preferably R₅' is monosubstituted by halogen, C₁₋₄alkyl (e.g. methyl), C₁₋₄alkoxy (e.g. methoxy), hydroxy or CF₃. For instance, when R₅' is C₃₋₁₈heterocycloalkyl, eg. piperidinyl, it may be substituted, preferably at the hetero atom thereof, e.g. as N-C₁₋₄alkyl-piperidinyl

Preferably R₁₀ is halogen.

Preferably X' is -NH-, -NH-Y'- or -O-.

The Invention includes the following compounds:

4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)imidazole;
 4-(4-Fluorophenyl)-5-(2-(3-bromophenylamino)-4-pyrimidinyl)imidazole;
 4-(4-Fluorophenyl)-5-(2-(3-hydroxyphenylamino)-4-pyrimidinyl)imidazole;
 4-(4-Fluorophenyl)-5-(2-(4-bromophenylamino)-4-pyrimidinyl)imidazole;
 4-(4-Fluorophenyl)-5-(2-(3-methoxyphenylamino)-4-pyrimidinyl)imidazole;
 4-(4-Fluorophenyl)-5-(2-(3-methylphenylamino)-4-pyrimidinyl)imidazole;
 4-(4-Fluorophenyl)-5-(2-(3-trifluoromethylphenylamino)-4-pyrimidinyl)imidazole;
 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-2-tert.butylimidazole;
 4-(4-Fluorophenyl)-5-(2-(3-fluorophenoxy)-4-pyrimidinyl)imidazole;
 2-(1-Aminocyclohexyl)-4-(4-fluorophenyl)-5-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole;
 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole;
 5-(4-Fluorophenyl)-2-(1-aminocyclohexyl)-4-(2-(3-methylphenyl-1-amino)-4-pyrimidinyl)-1-H-imidazole;
 5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)-ethyl]-4-(2-(R)-1-phenylethyl amino)-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)ethyl]-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)-ethyl]-4-(2-cyclohexylamino-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)-ethyl]-4-(2-cyclopropyl methylamino-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclohexylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclopropylmethylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cycloheptylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclopropylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclopentylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-ethylpiperidinyl)-4-(2-(S)-1-phenylethyl amino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-ethylpiperidinyl)-4-(2-cyclohexylamino-4-pyrimidinyl)-1-H- imidazole;

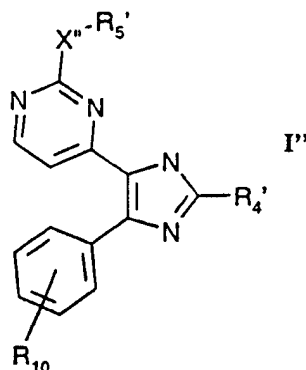
5-(4-Fluorophenyl)-2-(1-hydroxy-4-ethylpiperidinyl)-4-(2-cyclpropylmethyl amino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-n-butyloxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole, and

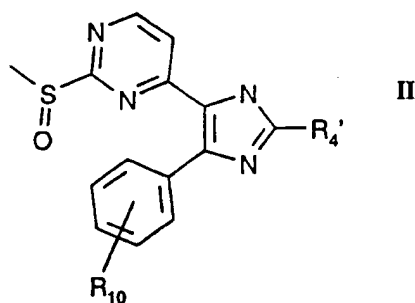
5-(4-Fluorophenyl)-2-(1-n-butyloxy-4-methylpiperidinyl)-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole.

The novel imidazoles of the invention, in particular the compounds of formulae I and I' and the specific compounds listed above are hereinafter referred to "Agents of the Invention".

Agents of the Invention of formula I''

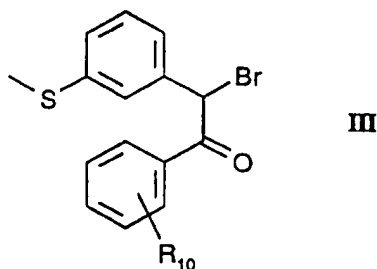


wherein R_4' , R_5' and R_{10} are as previously defined and X'' is -NH- or -O-, may be prepared by reacting the corresponding precursor compound of formula II



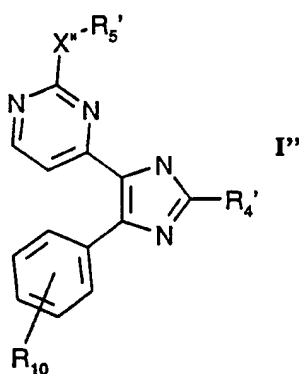
wherein R_4' and R_{10} are as previously defined, with the corresponding R_5' -NH₂ or R_5' -OH derivative. For example, the reaction may be carried out by refluxing the reactants in an organic solvent, e.g. dichloroethane, e.g. in the presence of diethoxytrifluoroborane.

The precursor compound of formula II may be prepared by controlled oxidation of the corresponding 5(2-methylthio-4-pyrimidinyl)-4-phenylimidazole, e.g. employing an oxidising agent such as mCPBA (meta chloroperbenzoic acid), conveniently in an organic solvent such as methylene chloride. The corresponding 5(2-methylthio-4-pyrimidinyl)-4-phenylimidazole compound may be prepared by contacting the corresponding acetophenone precursor compound of formula III

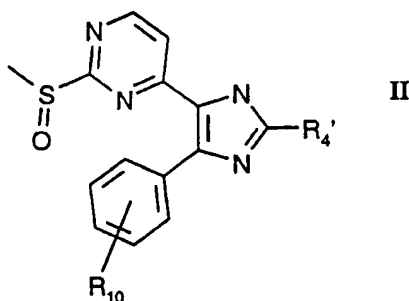


wherein R_{10} is as defined above, with a mixture of formic acid formamide and ammonium formate at elevated temperature, e.g. at a temperature of up to about 190°C . The compound of formula III may be prepared by bromination of the corresponding 2-(2-methylthio-4-pyrimidinyl)acetophenone. The 2-(2-methylthio-4-pyrimidinyl)acetophenone precursor may be prepared by reacting the corresponding N-methoxy-N-methylbenzamide with 4-methyl-2-(methylthio)pyrimidine, e.g. in a THF containing organic solvent with cooling.

Thus in a further aspect the invention includes a process for the preparation of a compound of formula I''

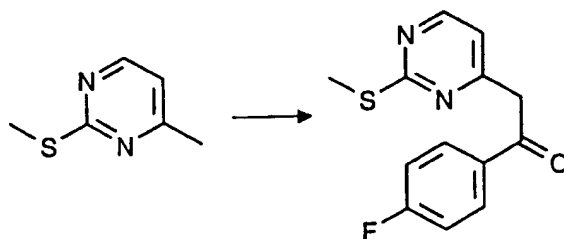


wherein R_4' , R_5' and R_{10} are as previously defined and X'' is $-\text{NH}-$ or $-\text{O}-$, which comprises reacting the corresponding precursor compound of formula II



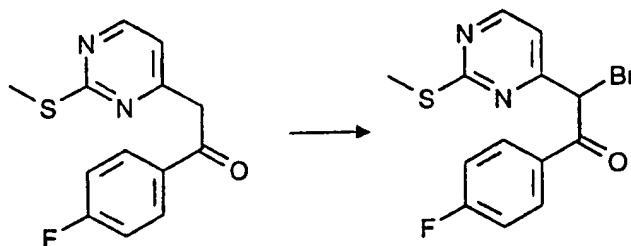
wherein R_4' and R_{10} are as previously defined, with the corresponding $R_5'-\text{NH}_2$ or $R_5'-\text{OH}$ derivative.

The synthesis of Agents of the Invention is further described in the following Examples.

EXAMPLES**Example 1: 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-1-H-imidazole****a) 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone**

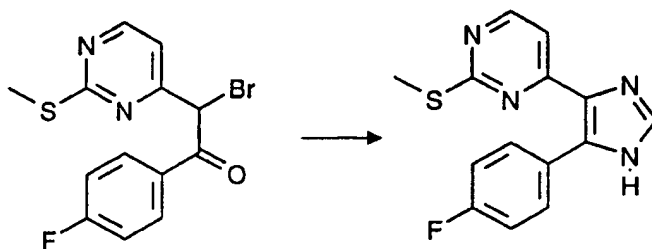
n-BuLi (10 ml of a 1.6 M solution in hexane; 12 mmol) is added at -78°C to a solution of diisopropylamine (2.48 ml; 17 mmol) in THF (15 ml) and stirred for 5 min. 4-Methyl-2-(methylthio)pyrimidine (2g; 14.5 mmol) dissolved in THF (2 ml) is added dropwise and stirred for 30 min at -78°C . 4-Fluoro-N-methoxy-N-methylbenzamide (2.66 g; 14.5 mmol) is dissolved in THF (3 ml) and added slowly to the reaction mixture. The mixture is warmed to r.t. within 45 min. and poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield 2.5 g (65%) of yellow crystals after recrystallisation from tert.butyl methyl ether/hexane.

$^1\text{H-NMR}$ (200 MHz CDCl_3): 3.00 (s, 3H); 6.30 (s, 1H; vinyl-H of enol); 7.00 (d, 1H); 7.50 (dd, 2H); 8.20 (dd, 2H); 8.7 (d, 2H). Due to pH-dependent keto-enol tautomerism, signals may be duplicated.

b) 4-Fluoro-2-bromo -2-(2-methylthio-4-pyrimidinyl)acetophenone

Bromine (1.22g; 7.6 mmol) in acetic acid (5.6 ml) is added to a solution of 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone (2g; 7.6 mmol) in acetic acid (40 ml). The initially thick precipitate is almost dissolved after 20 min., filtered and the filtrate evaporated to dryness. The residue is taken up in a saturated solution of NaHCO_3 and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield 2.6 g (100%) of a brown oil, which is used in the next step without purification.

c) 4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidinyl)-1-H-imidazole

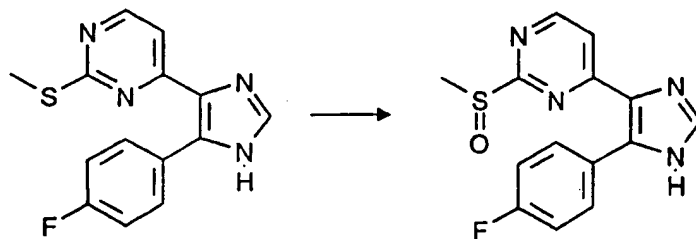


4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidinyl)acetophenone (0.2 g; 0.58 mmol) is dissolved in formic acid (2.6 ml), formamide (2.1 ml) and ammonium formate (2.6g) added and heated at 190 C for 20 min. The mixture is poured on water (100 ml), filtered, and the filtrate adjusted to pH ~10 with a saturated solution of Na_2CO_3 . A yellow precipitate is formed and yielded after washing with water and drying at high vacuum the title compound (63 mg; 38%).

$^1\text{H-NMR}$ (360 MHz DMSO-d_6): 2.18 (s, 3H); 7.28 (dd, 2H); 7.45-7.55 (bs, 1H); 7.65 (dd, 2H); 7.90 (s, 1H); 8.50 (d, 1H); 12.85 (bs, 1H).

FAB-MS (m/z): 287 (MH⁺).

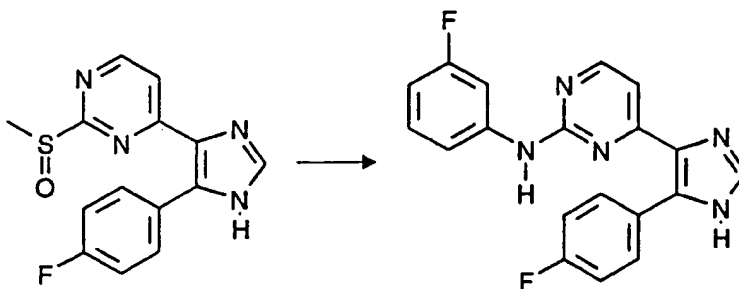
d) 4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-1-H-imidazole



4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidinyl)imidazole (0.1 g; 0.35 mmol) in methylene chloride (1 ml) is stirred and cooled to 5-10 C and mCPBA (55%, 0.33 g; 1.4 mmol) in methylene chloride (3 ml) added. The yellow, turbid mixture clears and becomes almost colorless and is

warmed up to r.t. A precipitate formed after ~1.5 hrs and is stirred for another 6 hrs. The precipitate is filtered off, washed with ether and yields the title compound (77 mg; 70%).
¹H-NMR (360 MHz DMSO-d₆): 3.05 (s, 3H); 7.28 (dd, 2H); 7.72 (dd, 2H); 8.00 (s, 1H); 8.05-8.20 (bs, 1H); 8.92 (d, 2H); 13.00 (bs, 1H).

e) 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-1-H-imidazole



4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole (0.05 g, 0.16 mmol) is dissolved in 1,2-dichloroethane (2 ml), 3-fluoroaniline (0.5 ml, 5.2 mmol) and BF₃·OEt₂ (0.02 ml; 0.16 mmol) added and the reaction mixture refluxed for 3.5 hrs. The mixture is taken up in 1N Na₂CO₃ and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over Na₂SO₄ and evaporated to dryness to yield a brown oil (520 mg), which is purified by silica gel chromatography (CH₂Cl₂/MeOH/NH₃ conc 97.5/2.5/0.25) and gives the title compound (10 mg; 18%) as off-white crystals.

¹H-NMR (400 MHz DMSO-d₆, 120 °C): 6.32 (dt, 1H); 7.02-7.08 (m, 3H); 7.15 (dd, 1H); 7.22 (td, 1H); 7.82 (dd, 2H); 7.88 (s, 1H); 8.20 (d, 1H); 9.00 (bs, 1H).

MS (m/z): 349 (M⁺).

The following compounds of Formula V identified in Table I are prepared analogously.

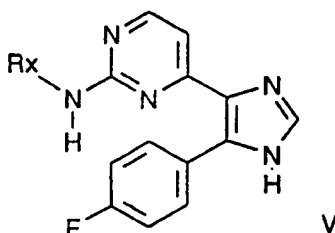
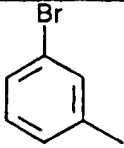
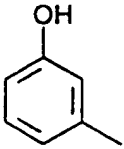
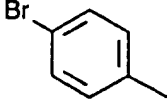
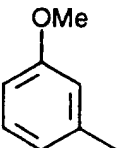
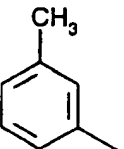
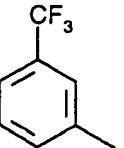
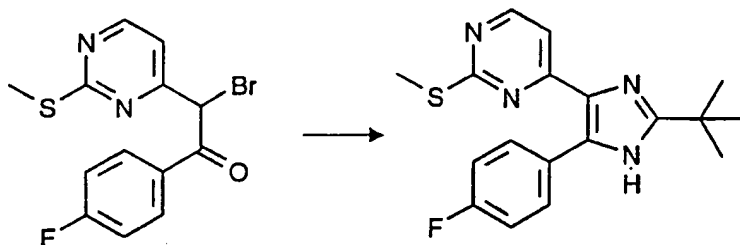


Table 1

Example No	Rx	Yield %	NMR/MS
2		66	<p>¹H-NMR (360 MHz DMSO-d₆, 120 C): 7.05 (bd, 1H); 7.15 (t, 2H); 7.52-7.60 (bs, 1H); 7.68-7.70 (dd, 2H); 7.78 (s, 1H); 7.82 (bs, 1H); 8.40 (d, 2H); 8.90 (bs, 1H).</p> <p>MS (m/z): 410 (M⁺)</p>
3		22	<p>¹H-NMR (400 MHz DMSO-d₆, 120 C): 6.38 (dd, 1H); 6.90 (t, 1H); 7.05 (dd, 1H); 7.10 (t, 2H); 7.70 (dd, 2H); 7.78 (s, 1H); 8.35 (d, 2H); 8.60 (bs, 1H).</p> <p>MS (m/z): 346 (M-H⁺); 347 (M⁺)</p>
4		10	<p>¹H-NMR (400 MHz DMSO-d₆, 120 C): 7.10 (t, 3H); 7.20 (d, 2H); 7.42 (d, 2H); 7.62 (dd, 2H); 7.78 (s, 1H); 8.39 (d, 2H); 8.90 (bs, 1H).</p> <p>MS (m/z): 409 (M-H⁺); 410 (M⁺)</p>
5		44	<p>¹H-NMR (400 MHz DMSO-d₆, 120 C): 3.70 (s, 3H); 6.44 (dd, 2H); 7.00 (t, 1H); 7.05-7.15 (m, 2H); 7.22 (bs, 1H); 7.65 (dd, 2H); 7.78 (s, 1H); 8.39 (dd, 2H); 8.75 (bs, 1H).</p> <p>MS (m/z): 346 (M-H⁺); 347 (M⁺)</p>
6		69	<p>¹H-NMR (360 MHz DMSO-d₆, 120 C): 2.15 (s, 3H); 6.68 (bd, 1H); 6.90 (bm, 2H); 7.18 (t, 2H); 7.2-7.4 (bm, 2H); 7.68 (dd, 2H); 7.89 (s, 1H); 8.43 (d, 2H); 9.25 (bs, 1H).</p> <p>MS (m/z): 344 (M-H⁺); 345 (M⁺)</p>
7		75	<p>¹H-NMR (400 MHz DMSO-d₆, 120 C): 7.10 (t, 2H); 7.15 (d, 1H); 7.23 (bt, 1H); 7.65 (dd, 2H); 7.78 (s, 1H); 7.83 (bd, 1H); 7.92 (bs, 1H); 8.42 (d, 2H); 9.18 (bs, 1H).</p> <p>FAB-MS (m/z): 400 (MH⁺)</p>

Example 8: 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-2-tert.butyl-4-pyrimidinyl)-1-H-imidazole

a) 4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidinyl)-2-tert.butyl-1-H-imidazole

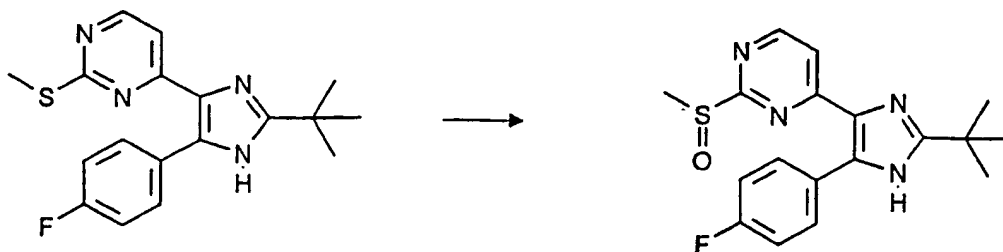


Pivalic acid (60 g, 538mmol) is melted by heating to 160 C. $(\text{NH}_4)_2\text{CO}_3$ (5 g, 52.7 mmol) is added portionwise and after completed addition the mixture is cooled to 80 C. 4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidinyl)acetophenone (3 g, 3.8 mmol), dissolved in ca 1g of pivalic acid, is added and the reaction mixture heated to 180 C for 10 min., poured on a saturated solution of Na_2CO_3 and extracted with tert.butylmethylether. The organic phase is washed with 2N HCl and the water phase made basic with a saturated solution of Na_2CO_3 and extracted with tert.butylmethylether. Purification by silica gel chromatography (ethyl acetate/hexane 15/85 to 20/80) yields the title compound as yellow crystals (762mg, 25%).

$^1\text{H-NMR}$ (360 MHz, CDCl_3): 1.50 (s, 9H); 2.62 (s, 3H); 6.92 (d, 1H); 7.15 (dd, 2H); 7.58 (dd, 2H); 8.27 (d, 2H), 9.91 (bs, 1H).

MS (m/z): 343 (MH⁺).

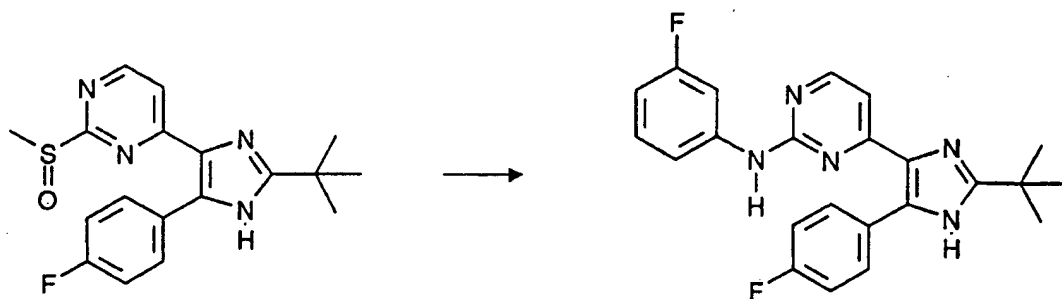
b) 4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-2-tert.butyl-1-H-imidazole



4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-2-tert.butylimidazole (0.4 g; 1.16 mmol) in methylene chloride (4 ml) is stirred and cooled to 5-10 C and mCPBA (55%, 0.48 g; 1.5 mmol) in methylene chloride (3 ml) added. After stirring at r.t. for 2 h, the reaction mixture is diluted with

ethyl acetate (30 ml) and washed once with 0.5N $\text{Na}_2\text{S}_2\text{O}_3$ (30 ml) and then twice with 1N NaOH. The organic phase is dried over Na_2SO_4 and evaporated to dryness to yield the title compound as light yellow crystals (397 mg, 95%), which are used without further purification.

c) 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-2-tert.butyl-1-H-imidazole

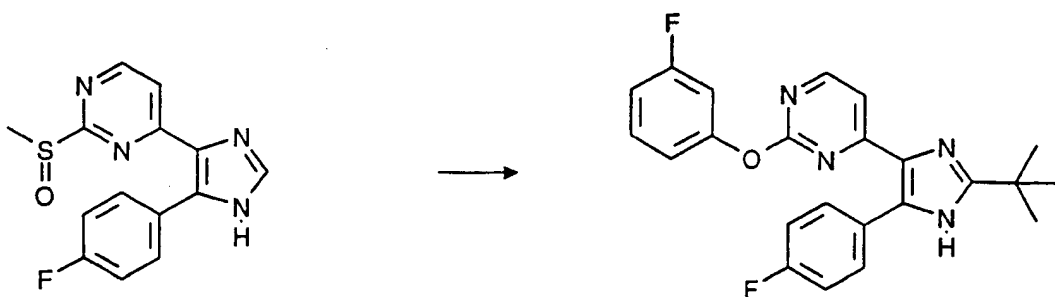


4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-2-tert.butylimidazole (0.2 g, 0.55 mmol), 3-fluoroaniline (1 ml, 10 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (0.07 ml, 0.5 mmol) are heated for 20 min. at 160 °C. The reaction mixture is diluted with tert.butylmethylether and washed with a solution of saturated Na_2CO_3 . The organic phase is dried over Na_2SO_4 , evaporated to dryness and the product purified over silica gel (acetone/hexane 3/7) to yield the title compound, which is recrystallised from methanol (181 mg, 80%).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6 , 120 °C): 1.50 (s, 9H); 6.60 (bs, 1H); 7.09 (dd, 2H); 7.15-7.30 (bs, 2H); 7.30-7.50 (bs, 2H); 6.05 (bs, 2H); 8.39 (bs, 2H); 11.60-11.70 (bs, 1-2H).

MS (m/z): 405 (M^+), 390 ($\text{M}-\text{CH}_3$).

Example 9 4-(4-Fluorophenyl)-5-(2-(3-fluorophenyloxy)-4-pyrimidinyl)-1-H-imidazole



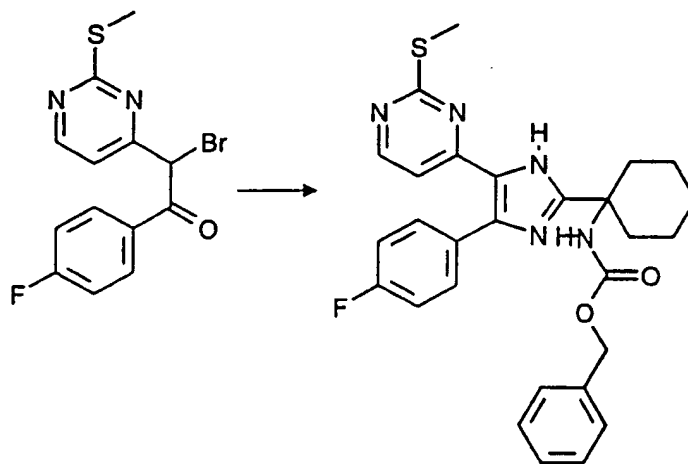
3-Fluorophenol (0.074 ml, 0.8 mmol) is added to a solution of $\text{KN}(\text{TMS})_2$ (0.88 ml of a 1.3 M solution in toluene; 0.66 mmol) in THF (3 ml) and is stirred for 5 min. 4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole (0.05 g, 0.16 mmol) is dissolved in warm THF (4 ml) and added rapidly to the reaction mixture, which is then stirred over night at room temperature. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4 , evaporated to dryness, and the product purified over silica gel (acetone/hexane 3/7 to 6/4) to yield the title compound (45 mg, 79%) as white crystals.

$^1\text{H-NMR}$ (360 MHz, DMSO-d_6): 6.95 (d, 1H); 7.05 (dd(=t), 2H); 7.37 (dd, 1H); 7.56 (d, 1H); 7.58 (d, 1H); 7.85 (s, 1H); 8.55 (dd, 1H).

MS (m/z): 350 (M^+), 349 (M-H).

Example 10 2-(1-Aminocyclohexyl)-4-(4-fluorophenyl)-5-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole

a) 5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-methylthio-4-pyrimidinyl)-1-H-imidazole

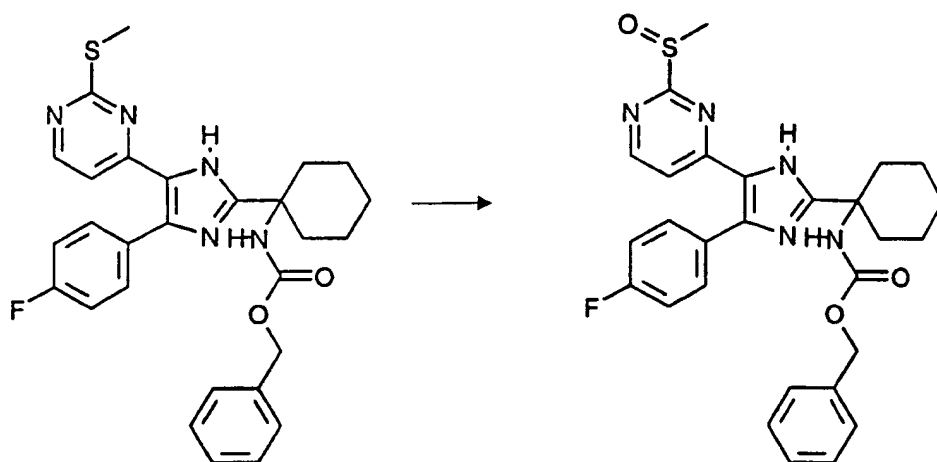


1-N-carbobenzyloxy-1-cyclohexanecarboxylic acid (E.Didier et al. Tetrahedron 1992, 48(39), 8471) (4.17g; 15mmol), and ammoniumcarbonate (Fluka; 1.46g; 15mmol) are dissolved in DMF (15ml) and heated to 110°C for 20min. until gas evolution ceases. After cooling to room temperature, 4-fluoro-2-bromo-2-(2-methylthio-4-pyrimidinyl)acetophenone (361mg; 1mmol) is added as a solid and the mixture heated to 125°C for 2h. The reaction mixture is poured on 1M Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over Na_2SO_4 , evaporated to dryness and chromatographed (SiO_2 ; acetone/hexane 15/85) to give the pure title compound as a yellow oil (0.26g; 51%).

¹H-NMR (400MHz; DMSO-d₆): Mixture of tautomers: 1.30-1.65 (m, 8H); 2.06 (s, 3H); 2.15-2.30 (m, 2H); 4.95 (bd, 2H); 5.18 (t, 1H); 7.18-7.40 (m, 9H); 7.50 (d, 1H); 8.48 (d, 0.8H); 8.51 (d, 0.2H).

MS (m/z): 517 (M⁺).

b) 5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-methylsulfinyl-4-pyrimidinyl)-1-H-imidazole

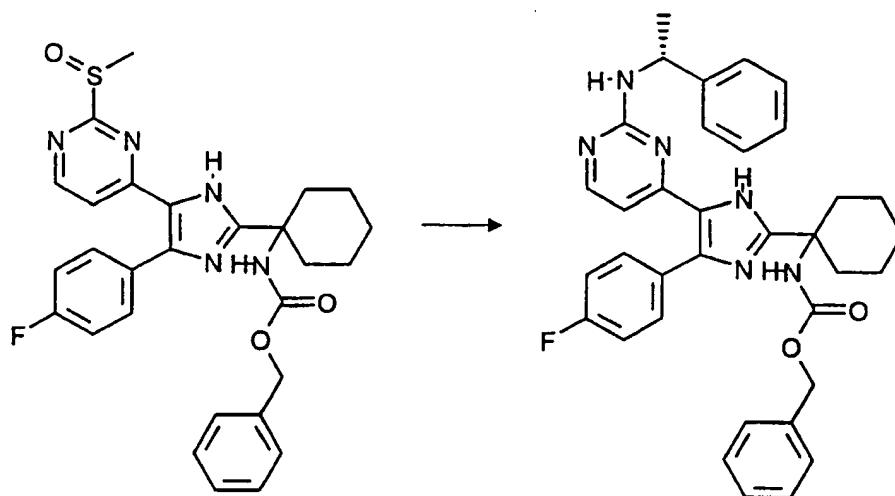


5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-methylthio-4-pyrimidinyl)imidazole (8.5g; 16.4mmol) is dissolved in methylene chloride (160ml) and cooled to 5°C under stirring, while mCPBA (4.46g; 21.86mmol) in methylene chloride (45ml) is added within 30min. After stirring for 15min., the reaction mixture is poured on 1M Na₂CO₃ and extracted twice with methylene chloride. The combined organic phases are dried over Na₂SO₄, evaporated to dryness and purified by chromatography (SiO₂; acetone/hexane 15/85) to yield the title compound as a yellow foam (5.6g; 62%).

¹H-NMR (400MHz; DMSO-d₆): Mixture of tautomers: 1.30-1.70 (m, 6H); 2.00-2.30 (m, 4H); 2.62 (s, 3H); 5.00 (s, 2H); 7.20-7.45 (m, 7H); 7.65-7.77 (m, 2H); 7.90 (d, 1H); 8.85 (d, 0.8H); 8.87 (d, 0.2H)

MS (m/z): 532.2 (M-H).

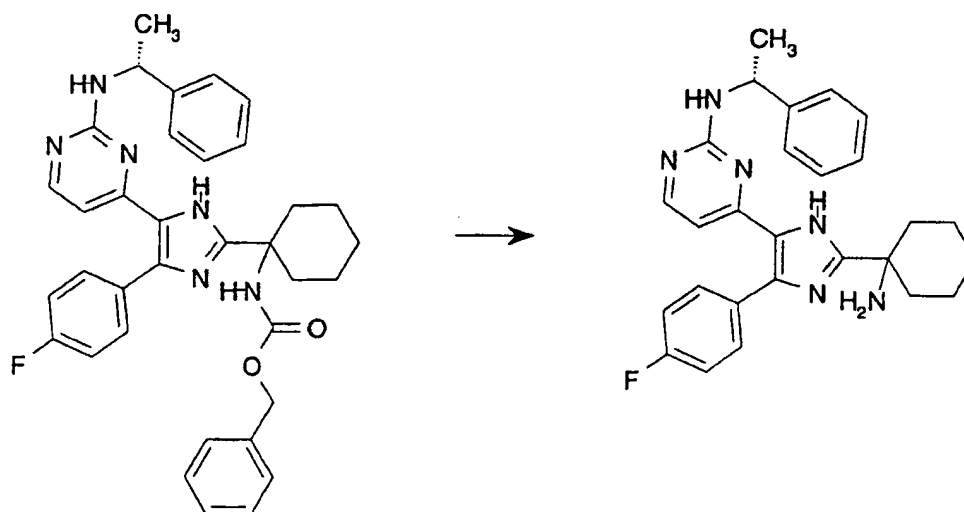
c) 5-(4-Fluorophenyl)-2-(1-N-carbobenzylloxycyclohexyl)-4-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole



5-(4-Fluorophenyl)-2-(1-N-carbobenzylloxycyclohexyl)-4-(2-methylsulfinyl-4-pyrimidinyl)imidazole (2g; 3.75mmol) and R(+)-1-phenylethylamine (2.27ml; 18.75mmol) are dissolved in toluene (75ml) and heated to 125°C for 48h. Toluene is evaporated and the residue chromatographed (SiO₂; acetone/cyclohexane 15/85) to yield the title compound as light yellow foam (1.6g; 72%).

MS (m/z): 591.3 (MH⁺).

d) 4-(4-Fluorophenyl)-2-(1-aminocyclohexyl)-5-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole



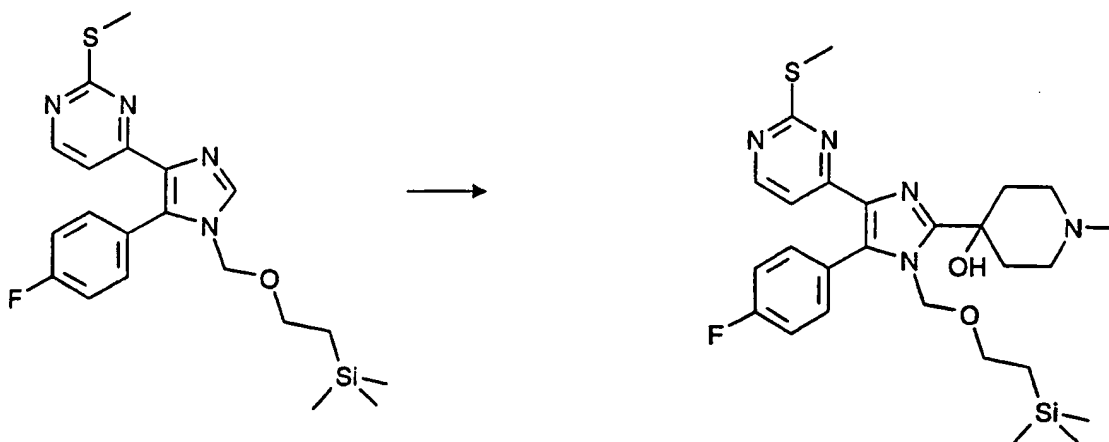
5-(4-Fluorophenyl)-2-(1-N-carbobenzoyloxycyclohexyl)-4-(2-(R-1-phenylethylamino)-4-pyrimidinyl)imidazole (1g; 1.7mmol) is dissolved in HOAc (60ml) and HBr/HOAc (33%; 6ml) added. The reaction mixture is stirred at 35°C for 90min. and then poured on water (500ml) and washed twice with ether. The water phase is made basic with a saturated solution of Na₂CO₃ and 2N NaOH and extracted with tert. butyl methyl ether three times. The combined organic phases are washed with water, dried over Na₂SO₄, evaporated to dryness and chromatographed (SiO₂; TBME/MeOH/NH₃conc. 96/4/0.4) to yield the title compound as a white foam, which is crystallised from ether (574mg; 75%).

¹H-NMR (400MHz; DMSO-d₆, 120°C): 1.42 (d, 3H); 1.50-1.80 (m, 8H); 2.10 (bt, 2H); 5.00 (dq, 1H); 6.58 (d, 1H); 6.85 (d, 1H); 7.10-7.20 (m, 2H); 7.22-7.32 (m, 5H); 7.65-7.71 (m, 2H); 8.15 (d, 1H).

MS (m/z): 457 (MH⁺).

Example 11 **5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-phenylethylamino-4-pyrimidinyl)-1-H- imidazole**

a) 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylthio-4-pyrimidinyl)-1-(trimethylsilylethylloxymethyl)imidazole

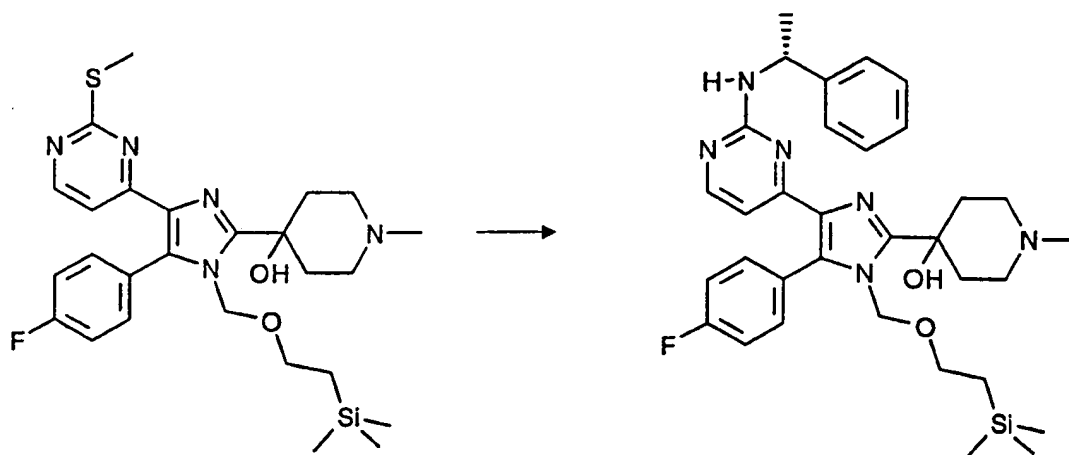


5-(4-Fluorophenyl)- 4-(2-methylthio-4-pyrimidinyl)-1-(trimethylsilylethylloxymethyl)imidazole (7.1g; 17mmol) is dissolved in THF (80ml) and cooled to -78°C. n-BuLi (12.7ml of a 1.6M solution; 20mmol) is added and the reaction stirred for 10min at -78°C. N-methyl-4-piperidone (2.6g; 22mmol) is added rapidly and after stirring for 5 minutes at -78°C, the reaction mixture is poured on a saturated solution of NaCl and extracted 3x with ethyl acetate. The combined organic phases are dried over Na₂SO₄ and evaporated to dryness to render the crude

product, which is purified by silica gel chromatography (tert.butyl methyl ether/methanol/NH₃ conc 97:3:0.2) to yield the title compound as yellow solid (5.35g; 59%).

¹H-NMR (200 MHz; CDCl₃): 0.00 (s, 9H); 0.82 (dd, 2H); 1.97 (s, 3H); 1.98-2.10 (bd, 2H); 2.40 (s, 3H); 2.47-2.61 (m, 4H); 2.70-2.88 (m, 2H); 3.33 (dd, 2H); 5.30 (s, 2H); 7.20 (dd, 2H); 7.43 (dd, 2H); 7.65 (d, 1H); 8.42 (d, 1H).

b) 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-(trimethylsilylethoxymethyl)imidazole



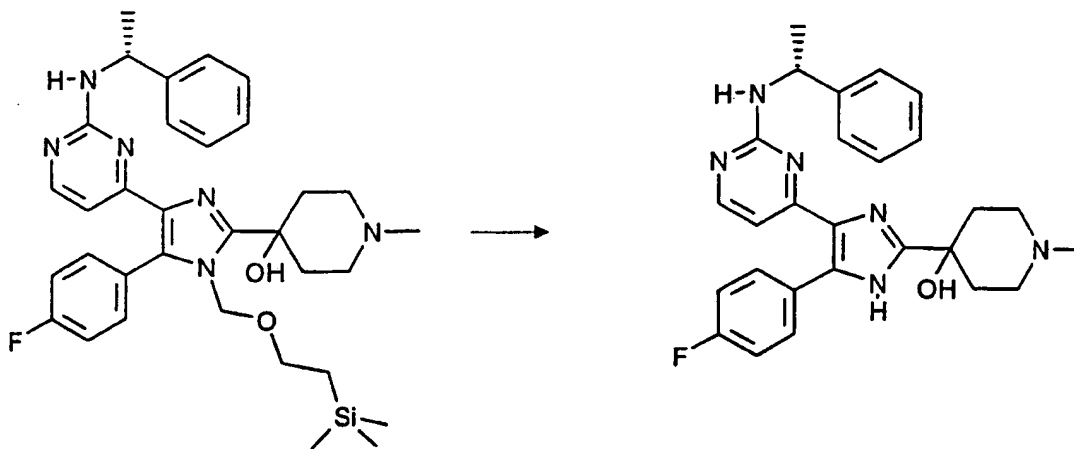
5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylthio-4-pyrimidinyl)-1-(trimethylsilylethoxymethyl)imidazole (32.7 g; 0.06 mol) was dissolved in methylene chloride (200 ml), HOAc (50 ml) added and cooled to 0° C. mCPBA (19 g; 70%, 0.077 mol) in methylene chloride (120 ml) was added dropwise within 5 min. After stirring for another 5 min. the reaction mixture was poured on a saturated solution of Na₂CO₃ and extracted with ethyl acetate three times. The combined organic phases were dried over Na₂SO₄ and evaporated to dryness to render the crude product, which was filtered through silica gel (TBME/MeOH/NH₃conc. 80/20/3). The solid product was washed with TBME and yielded pure 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylsulfinyl-4-pyrimidinyl)-1-(trimethylsilylethoxymethyl)imidazole (24.2 g; 72%).

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylsulfinyl-4-pyrimidinyl)-1-(trimethylsilylethoxymethyl)imidazole (2.1g; 3.8mmol), R(+)-1-phenylethylamine (25ml) and toluene (25 ml) are heated to 140°C for 2h. Toluene and excess R(+)-1-phenylethylamine are distilled off at 0.1 mm Hg and the residue purified by silica gel chromatography (acetone/methanol 90/10 to 95/5) to deliver 1.1g (47%) of the title compound as colorless crystals.

¹H-NMR (360MHz; DMSO-d₆): -0.06 (s, 9H); 0.72 (bt, 2H); 1.16 (bs, 3H); 1.93-2.03 (m, 2H); 2.20 (s, 3H); 2.16-2.28 (m, 2H); 2.36 (bt, 2H); 2.53 (bt, 2H); 3.19-3.27 (m, 2H); 4.18-4.35 (bs, 1H); 5.30-5.43 (dd, 2H); 5.48 (s, 1H; OH); 6.97-7.05 (bs, 1H); 7.06-7.18 (m, 4H); 7.21-7.26 (t, 2H); 7.29-7.34 (t, 2H); 7.50-7.56 (t, 2H); 8.17 (d, 1H).

FAB-MS (m/z): 603 (MH⁺)

c) 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-phenylethylamino-4-pyrimidinyl)-1-H- imidazole



5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-(trimethylsilylethoxymethyl)imidazole (740mg, 1.23mmol) is dissolved on EtOH (10ml) and hydrochloric acid (aqueous, 37%, 10ml) and kept at room temperature for 20 minutes. The reaction mixture is then poured on a saturated solution of Na₂CO₃ and extracted with ethyl acetate. The resulting yellow foam is triturated with tert.butyl methyl ether/diethyl ether and the solid obtained is filtered off to provide the title compound (514mg; 88.7%) as yellow powder.

¹H-NMR (400MHz; DMSO-d₆; 120°C): 1.3-1.52 (bm, 3H); 1.85 (bd, 2H); 2.15-2.30 (m, 2H); 2.25 (s, 3H); 2.43-2.61 (m, 4H); 4.5 (bs, 1H); 7.10-7.45 (m, 8H); 7.66 (dd, 2H); 8.15 (d, 1H).

FAB-MS (m/z): 473 (MH⁺, 100); 453 (25); 308 (45).

The compounds of Examples 12-17 of Formula VI identified in Table 2 below are prepared by analogy with Example 10 and similarly the compounds of Examples 18-26, also of formula VI and as identified in Table 2, are prepared by analogy with Example 11.

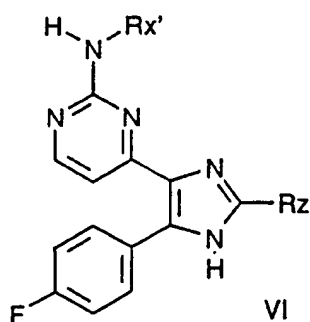
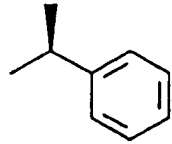
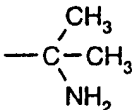
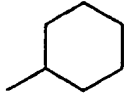
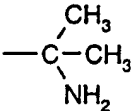
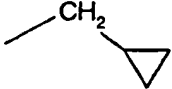
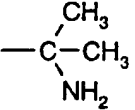
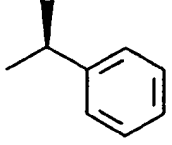
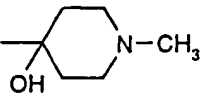
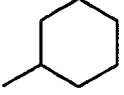
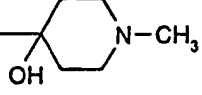
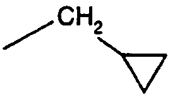
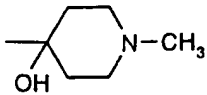
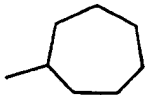
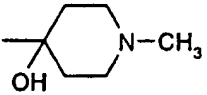

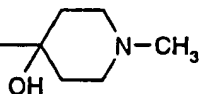
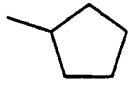
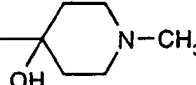
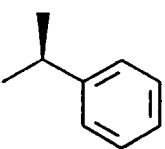
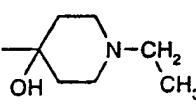
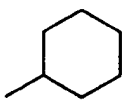
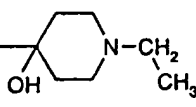


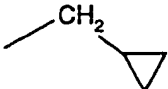
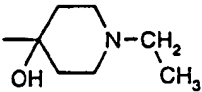
Table 2

Example No	Rx'	Rz	NMR/MS
12			NMR as Example 10 MS (m/z) ESI: 457 (MH ⁺ , 100)
13			¹ H-NMR (400MHz; DMSO-d ₆): 1.25-1.77 (m, 10H); 2.04 (bt, 2H); 2.15 (s, 3H); 6.65 (d, 1H); 6.91 (bt, 1H); 7.05 (bs, 1H); 7.17 (t, 2H); 7.26 (bd, 1H); 7.38 (bs, 1H); 7.63 (dd, 2H); 8.38 (d, 1H); 9.27 (bs, 1H). MS (m/z) EI: 442 (100); 425 (70); 413 (30); 399 (30).
14			¹ H-NMR (400MHz; CDCl ₃): 1.61 (s, 9H); 1.71-1.98 (bs, 2H, NH ₂); 5.10 (bs, 1H); 5.53 (bs, 1H, NH); 6.55 (bs, 1H); 7.11 (bt, 2H); 7.26 (d, 1H); 7.38 (dd, 2H); 7.45 (bd, 2H); 7.56 (dd, 2H); 8.07 (d, 1H); 10.00 (bs, 1H, NH). MS (m/z) EI: 416 (M ⁺ , 10); 399 (100); 384 (90); 294 (30); 120 (30); 105 (50).

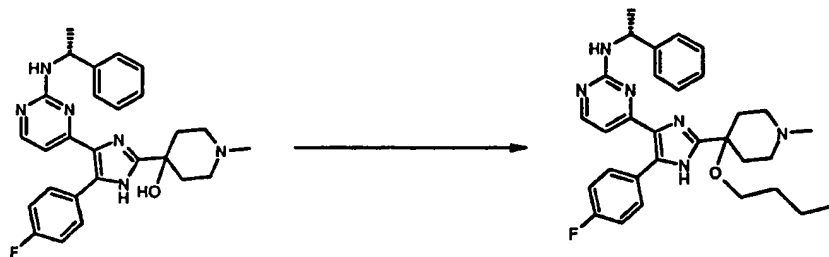
15			As for Example 14
16			<p>¹H-NMR (400MHz; DMSO-d₆; 120° C). 1.13-1.30 (m, 5H); 1.51 (s, 6H); 1.53-1.60 (m, 1H); 1.65-1.72 (m, 2H); 1.75-1.85 (m, 2H); 3.52-3.62 (m, 1H); 5.25 (s, 1H); 5.87 (s, 1H); 6.85 (d, 1H); 7.12-7.20 (m, 2H); 7.65-7.71 (m, 2H); 8.15 (s, 1H).</p> <p>MS (m/z) ESI: 395.2 (MH⁺).</p>
17			<p>¹H-NMR (400MHz; DMSO-D₆). Mixture of rotamers with broad signals: -0.06-0.13 (bs, 2H); 0.26-0.40 (bs, 2H); 0.72-0.97 (bs, 1H); 1.47 (s, 6H); 2.80-3.05 (bs, 2H, NH₂); 3.13-3.45 (bm, 2H); 6.78-7.05 (bs, 2H); 7.22 (bt, 2H); 7.68 (bt, 2H); 8.17 (d, 1H); 12.00 (bs, 1H, NH).</p>
18			as for Example 11
19			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 0.88-1.28 (m, 6H); 1.45-1.73 (m, 4H); 1.80-1.90 (m, 2H); 2.09-2.18 (bt, 2H); 2.19 (s, 3H); 2.32-2.45 (m, 2H); 2.46-2.52 (m, 2H); 2.60-2.70 (bs, 1H); 5.13 (bs, 0.7H); 5.25 (bs, 0.3H); 6.50 (bs, 1H); 6.85 (bd, 1H); 7.00 (bs, 1H); 7.13-7.27 (m, 2H); 7.55-7.70 (m, 2H); 8.18 (bt, 1H).</p> <p>MS (m/z) ESI: 449.2 (MH⁺, 100).</p>

20			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 0.00 (bs, 1H); 0.13 (bs, 1H); 0.30 (bs, 1H); 0.38 (bs, 1H); 0.80 (bs, 0.7H); 0.95 (bs, 0.3H); 1.84 (bd, 2H); 2.13 (bt, 2H); 2.20 (s, 3H); 2.38 (bt, 2H); 2.49 (bd, 2H); 2.75 (bs, 2H); 3.05 (bs, 1H); 5.15 (bs, 0.7H); 5.27 (bs, 0.3H); 6.75 (bs, 1H); 7.05 (bs, 1H); 7.20 (bt, 2H); 7.65 (bs, 2H); 8.17 (d, 1H).</p> <p>MS (m/z) ESI: 421.2 (MH⁺, 100).</p>
21			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 0.92-1.69 (m, 12H); 1.83 (bd, 2H); 2.12 (bt, 2H); 2.21 (s, 3H); 2.38 (bt, 2H); 2.50 (bd, 2H); 3.50-3.80 (bs, 1H); 5.15 (bs, 0.7H, OH); 5.26 (bs, 0.3H, OH); 6.58 (bs, 1H, NH); 6.89 (bd, 0.3H); 7.02 (bs, 0.7H); 7.23 (bt, 2H); 7.62 (bs, 2H); 8.18 (d, 1H).</p> <p>MS (m/z) EI: 464 (M⁺, 50); 446 (100); 72 (55).</p>
22			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 0.30-0.68 (m, 4H); 1.85 (bd, 2H); 2.13 (bt, 2H); 2.20 (s, 3H); 2.38 (bt, 2H); 2.52 (bd, 2H); 2.65-2.80 (m, 1H); 5.17 (bs, 0.6H, OH); 5.26 (bs, 0.4H, OH); 6.71 (bs, 0.4H, NH); 6.95 (bs, 0.6H, NH); 7.08 (bs, 0.7H); 7.20 (bt, 2H); 7.26 (bs, 0.3H); 7.78 (bt, 2H); 8.20 (bd, 1H).</p> <p>MS (m/z) EI: 408 (M⁺, 70); 390 (100); 338 (40); 295 (20); 72 (50).</p>

23			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 1.12-1.71 (m, 8H); 1.85 (bd, 2H); 2.13 (bt, 2H); 2.19 (s, 3H); 2.38 (bt, 2H); 2.48 (bd, 2H); 3.51-3.78 (bs, 1H); 5.16 (bs, 0.7H, OH); 5.27 (bs, 0.3H, OH); 6.68 (bs, 1H); 6.95-7.08 (bd, 1H, NH); 7.71 (bt, 2H); 7.63 (bs, 2H); 8.17 (d, 1H).</p> <p>MS (m/z) EI: 436 (M⁺, 50); 418 (100); 366 (25); 72 (35).</p>
24			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 1.03 (bt, 3H); 1.30 (bs, 2.1H); 1.42 (bs, 0.9H); 1.86 (bd, 2H); 2.12 (bt, 2H); 2.30-2.47 (m, 4H); 2.55 (bd, 2H); 4.63 (bs, 0.6H); 5.04 (bs, 0.4H); 5.14 (s, 0.7H, OH); 5.28 (s, 0.3H, OH); 6.68 (bs, 1H, NH); 7.03 (bs, 1H); 7.10-7.48 (m, 7H); 7.66 (bs, 2H); 8.18 (bd, 1H).</p> <p>MS (m/z) EI: 486 (M⁺, 40); 468 (100); 86 (35).</p>
25			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 0.88-1.30 (m, 7H with sharp triplet at 1.03; (3H)); 1.45-1.73 (m, 6H); 1.85 (bd, 2H); 2.13 (bt, 2H); 2.29-2.47 (m, 4H with sharp quartet at 2.34 (2H)); 2.56 (bs, 2H); 3.06-3.28 (bs, 1H); 5.13 (s, 0.7H, OH); 5.23 (s, 0.3H, OH); 6.51 (bs, 0.6H, NH); 6.85 (bs, 0.4H, NH); 7.01 (bs, 1H); 7.22 (bt, 2H); 7.62 (bs, 2H); 8.17 (d, 1H).</p> <p>MS (m/z) EI: 464 (M⁺, 35); 446 (100), 86 (30).</p>

26			<p>¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: -0.10-0.45 (m, 4H); 0.65-0.91 (bs, 1H); 1.03 (t, 3H); 1.84 (bd, 2H); 2.12 (bt, 2H); 2.30-2.47 (m, 4H with quartett at 2.36 (2H)); 2.57 (bs, 2H); 2.65-2.90 (bs, 1H); 2.95-3.22 (bs, 1H); 5.15 (s, 0.7H, OH); 5.26 (s, 0.3H, OH); 6.77 (bs, 1H, NH); 7.08 (bs, 1H); 7.23 (bt, 2H); 7.65 (bs, 2H); 8.18 (d, 1H).</p> <p>MS (m/z) EI: 436 (M⁺, 70); 418 (100); 352 (30); 86 (10).</p>
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Example 27: 5-(4-Fluorophenyl)-2-(1-n-butyl-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole



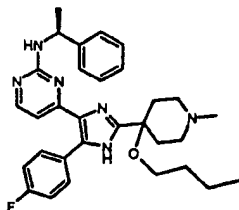
5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole (Example 11) (430 mg; 0.911 mmol), 1-butanol (30 ml) and H₂SO₄ (360 mg; 3.6 mmol) are refluxed for 4.5 h and evaporated to dryness. The residue is taken up in a saturated solution of Na₂CO₃ and extracted with ethyl acetate three times. The combined organic phases are dried over Na₂SO₄, filtered, evaporated and purified via SiO₂ chromatography (TBME/MeOH/NH₃ conc 98/2/0.2 to 96/4/0.2) to yield the title compound as colorless crystals (198 mg; 41%).

¹H-NMR (400MHz; DMSO-d₆). Mixture of rotamers with broad signals: 0.78-0.83 (m, 3H); 1.21-1.49 (m, 7H); 2.05-2.13 (bs, 4H); 2.17 (s, 3H); 2.25-2.48 (m, 4H); 3.05-3.16 (bq, 2H); 4.48-4.72 (bs, 0.6 H); 4.95-5.13 (bs, 0.4H); 6.90-7.10 (bs, 2H); 7.10-7.33 (m, 6H); 7.53-7.70 (m, 2H); 8.18 (d, 1H); 12.00 (bs, 1H, NH); 13.00 (bs, 1H, NH).

MS (m/z) EI: 428 (M⁺; 20); 471 (55); 455 (100).

The compound of Example 28 is prepared by analogy with example 27 from the compound of Example 18.

Example 28: 5-(4-Fluorophenyl)-2-(1-n-butyloxy-4-methylpiperidinyl)-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole



The title compound is the enantiomer of example 27. Their NMR- and MS-spectras are identical.

The Agents of the Invention, as defined above, e.g., of formula I, particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

In particular Agents of the Invention possess p38 MAP kinase (Mitogen Activated Protein Kinase) inhibiting activity. Thus the Agents of the Invention act to inhibit production of inflammatory cytokines, such as TNF- α and IL-1, and also to potentially block the effects of these cytokines on their target cells. These and other pharmacological activities of the Agents of the Invention as may be demonstrated in standard test methods for example as described below:

p38 MAP kinase Assay

The substrate (GST-ATF-2; a fusion protein comprising amino acids 1-109 of ATF-2 and the GST protein obtained by expression in E. coli) is coated onto the wells of microtiter plates (50 μ l/well; 1 μ g/ml in PBS/0.02% Na azide) overnight at 4 °C. The following day, the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide and are blocked with PBS/2% BSA/0.02% Na Azide for 1 h at 37 °C. Plates are washed again 4 times with PBS/0.5% Tween 20/0.02% Na azide. The kinase cascade reaction is then started by adding the following reactants in 10 μ l aliquots to a final reaction volume of 50 μ l.

1. Agents of the Invention titrated from 10 to 0.001 μ M in 10-fold dilutions or solvent (DMSO) or H₂O.
2. Kinase buffer (5x); pH 7.4; 125 mM Hepes (Stock at 1M; Gibco #15630-056), 125 mM β -glycerophosphate (Sigma #G-6251); 125 mM MgCl₂ (Merck #5833); 0.5 mM Sodium orthovanadate (Sigma #5-6508), 10 mM DTT (Boehringer Mannheim #708992). The (5x) kinase buffer must be prepared fresh the day of the assay from 5x stock solutions kept at RT. DTT is kept at -20 °C and is added as the last reagent.
3. His-p38 MAP kinase (10 ng/well; Novartis - a fusion protein comprising full length murine p38 MAP kinase and a His tag, obtained by expression in *E. coli*)
4. cold ATP (final concentration 120 μ M; Sigma #A-9187)
5. Water

After 1h at 37 °C the kinase reaction is terminated by washing the plates four times as previously described. Phosphorylated GST-ATF-2 is then detected by adding:

1. the PhosphoPlus ATF-2 (Thr71) Antibody (50 μ l/well; 1/1000 final dilution in PBS/2% BSA/0.02% Na Azide; New England Biolabs #9221L) for 90 min at RT.
2. Biotin labelled goat-anti-rabbit IgG (50 μ l/well; 1/3000 final dilution in PBS/2% BSA/0.02% Na Azide; Sigma #B-9642) for 90 min at RT.
3. Streptavidin-alkaline phosphatase (50 μ l/well; 1/5000 dilution in PBS/2% BSA/0.02% Na Azide; Jackson ImmunoResearch #016-050-084) for 30 min at RT.
4. Substrate (100 μ l/well; Sigma 104 Phosphatase substrate tablets, 5 mg/tablet; #104-105; 1 mg/ml in substrate buffer, Diethanolamine (97 ml/l; Merck #803116) + MgCl₂·6H₂O (100 mg/l; Merck #5833) + Na Azide (0.2 g/l) + HCl 1M to pH 9.8) 30 min at RT.

After step 1,2 and 3 the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide. After step 4, the plates are read in a Bio-Rad microplate reader in a dual wavelength mode (measurement filter 405 nm and reference filter 490 nm). The background value (without ATP) is subtracted and IC₅₀ values are calculated using the Origin computer program (4 parameter logistic function).

Agents of the Invention typically have IC₅₀s for p38 MAP kinase inhibition in the range from about 100 nM to about 10 nM or less when tested in the above assay.

Assay for Inhibition of TNF- α release from hPBMCs

Human peripheral blood mononuclear cells (hPBMCs) are prepared from the peripheral blood of healthy volunteers using ficoll-hypaque density separation according to the method of Hansell et al., J. Imm. Methods (1991) 145: 105. and used at a concentration of 10^5 cells/well in RPMI 1640 plus 10% FCS. Cells are incubated with serial dilutions of the test compounds for 30 minutes at 37°C prior to the addition of IFN γ (100 U/ml) and LPS (5 mg/ ml) and subsequently further incubated for three hours. Incubation is terminated by centrifugation at 1400 RPM for 10 min. TNF- α in the supernatant is measured using a commercial ELISA (Innotest hTNFa, available from Innogenetics N.V., Zwijnaarde, Belgium). Agents of the Invention are tested at concentrations of from 0 to 10 mM. Exemplified Agents of the Invention typically suppress TNF release in this assay with an IC₅₀ of from about 500 nM to about 50 nM or less when tested in this assay.

Assay for Inhibition of TNF- α Production in LPS stimulated mice

Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF- α) into the periphery. This model is be used to analyse prospective blockers of TNF release in vivo.

LPS (20 mg/kg) is injected i.v. into OF1 mice (female, 8 week old). One (1) hour later blood is withdrawn from the animals and TNF levels are analysed in the plasma by an ELISA method using an antibody to TNF- α . Using 20 mg/kg of LPS levels of up to 15 ng of TNF- α / ml plasma are usually induced. Compounds to be evaluated are given either orally or s.c. 1 to 4 hours prior to the LPS injection. Inhibition of LPS-induced TNF-release is taken as the readout.

Agents of the Invention typically inhibit TNF production to the extent of up to about 50% or more in the above assay when administered at 10 mg/kg p.o.

As indicated in the above assays Agents of the Invention are potent inhibitors of TNF- α release. Accordingly, the Novel Compounds have pharmaceutical utility as follows:

Agents of the Invention are useful for the prophylaxis and treatment of diseases or pathological conditions mediated by cytokines such as TNF α and IL-1, e.g., inflammatory

conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection, e.g. for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants and for the prevention of graft-versus-host disease, such as following bone marrow transplants.

Agents of the Invention are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Agents of the Invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways.

Agents of the Invention are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by TNF, especially by TNF α , e.g., acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe burns; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS-related cachexia, e.g., associated with or consequential to HIV infection.

Agents of the Invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides.

For the above indications the appropriate dosage will, of course, vary depending, for example, on the particular Agent of the Invention employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are obtained at daily dosages of from about 1 to about 10mg/kg/day p.o.. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 50 to about 750mg of Novel Compound administered orally once or, more suitably, in divided dosages two to four times/day.

The Novel Compounds may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Novel Compounds may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg Novel Compound per unit dosage.

In accordance with the foregoing the present invention also provides in a further series of embodiments:

A. A method of inhibiting production of soluble TNF, especially $\text{TNF}\alpha$, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, or alleviating one or more symptoms of any of the above mentioned conditions.

B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or

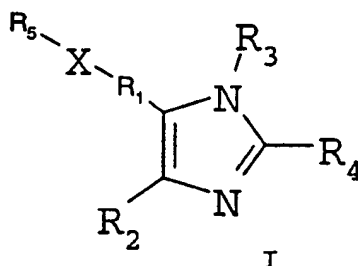
treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

CLAIMS

1. A 4-phenyl-5-(2-aryl-X)-4-pyrimidinyl-, 4-phenyl-5-(2-cycloalkyl-X)-4-pyrimidinyl-, 4-phenyl-5-(2-aralkyl-X)-4-pyrimidinyl- or 4-phenyl-5-(2-cycloalkylalkyl-X)-4-pyrimidinyl-imidazole, in which the 5-pyrimidinyl substituent is aryl, cycloalkyl, aralkyl or cycloalkylalkyl substituted directly via a heteroatom X selected from N, O or S, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof..
2. A compound according to claim 1 of formula I



wherein

R₁ is pyrimidinyl;

X is -NR₆-Y-, -O- or -S-,

where R₆ is H, C₁₋₄alkyl, C₆₋₁₈aryl, C₃₋₁₈heteroaryl, C₇₋₁₉aralkyl or C₄₋₁₉heteroaralkyl, and -Y- is C₁₋₄alkylene or a direct bond ;

R₂ is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF₃,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C₁₋₄alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C₁₋₄alkyl C₁₋₄alkylcarbonyl or C₁₋₄alkylthiocarbonyl substituted,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C₁₋₁₀alkoxy, C₂₋₁₀alkenoxy, C₂₋₁₀alkynoxy, C₃₋₇cyclalkoxy, C₅₋₇cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester, optionally mono- or di-C₁₋₄alkyl-substituted-C₀₋₁alkyl optionally C₁₋₄alkyl- or C₃₋₅cycloalkyl-substituted-carbonyl or -thiocarbonyl, optionally halo-substituted-C₁₋₄alkoxy, C₂₋₄alkenoxy, C₂₋₄alkynoxy, C₃₋₅cycloalkoxy or C₃₋₅cyclothioalkoxy, optionally halo substituted C₁₋₄ alkyl, oxycarbonyl or optionally N-C₁₋₄alkyl-substituted aminocarbonyl both of which are optionally C₁₋₄alkyl or C₃₋₅cycloalkyl substituted (including thiocarbonyl analogues thereof), optionally mono- or di-C₁₋₄alkyl-substituted-C₀₋₁alkylamine which is optionally mono-or di-N-C₁₋₄ alkyl substituted, optionally mono- or di-C₁₋₄alkyl-substituted-C₀₋₁alkyl optionally N-C₁₋₄alkyl-substituted amino-carbonyl or -thiocarbonyl, optionally N-C₁₋₄alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C₁₋₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁₋₄alkyl C₁₋₄alkylcarbonyl or C₁₋₄alkylthiocarbonyl substituted, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C₁₋₄alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl,

optionally mono- or di-N-C₁₋₄alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C₁₋₄alkyl C₁₋₄alkylcarbonyl or C₁₋₄alkylthiocarbonyl substituted;

R₃ is hydrogen,

heterocyclyl,

heterocyclylC₁₋₁₀alkyl,

optionally halo substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, aryl, aryl C_{1-10} alkyl, heteroaryl, or heteroaryl C_{1-10} alkyl,

optionally mono-or di- C_{1-4} alkyl-substituted C_{0-10} alkyl-oxycarbonyl or -oxythiocarbonyl optionally substituted by C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, or optionally mono-or di- C_{1-4} alkyl-substituted C_{1-10} alkyl

-cyano,

-nitro,

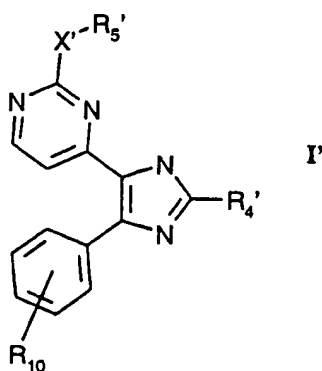
-hydroxy, - C_{1-10} alkoxy, - C_{3-7} cycloalkoxy, -heterocycloxy, -heterocyclyl C_{1-10} alkoxy, -aryloxy, -aryl C_{1-10} alkoxy, -heteroaryloxy, -heteroaryl C_{1-10} alkoxy (and thio oxy analogues thereof),

optionally substituted amino, carboxylate, thiocarboxylate, carbonyl or thiocarbonyl, sulphinyl or sulphonyl;

R_4 is H, or C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-18} heterocycloalkyl, C_{6-18} aryl, or C_{3-18} heteroaryl all optionally substituted by up to 4 substituents separately selected from alkyl, halogen, halo-substitued-alkyl, hydroxy, alkoxy, alkylthio, or optionally substituted amino;

R_5 is C_6-C_{18} aryl, C_3-C_{18} heteroaryl, or C_3-C_{12} cycloalkyl optionally substituted by up to 3 substituents separately selected from alkyl, halogen, halo-substitued-alkyl, hydroxy, alkoxy, alkylthio, optionally substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

3. A compound according to claim 1 of formula I'



wherein

R₅' is phenyl or C₃-C₇cycloalkyl each of which is optionally mono-substituted by halogen, C₁₋₁₀alkyl, C₁₋₁₀alkoxy, hydroxy, trihalomethyl or -NR₇R₈, where R₇ and R₈ are independently H, C₁₋₆alkyl, C₆₋₁₀aryl, C₆₋₁₀heteroaryl, C₇₋₁₁aralkyl or C₇₋₁₁heteroaralkyl;

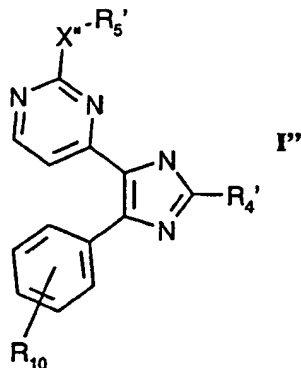
R₁₀ is halogen, cyano, amido, thioamido, amino or C₁₋₆alkyl;

R₄' is H, C₁₋₆alkyl, 1-hydroxyC₁₋₁₀alkyl, 1-C₁₋₆alkoxyC₁₋₁₀alkyl, 1-aminoC₁₋₁₀alkyl, 1-hydroxyC₃₋₁₀cycloalkyl, 1-C₁₋₆alkoxyC₃₋₁₀cycloalkyl, 1-aminoC₃₋₁₀cycloalkyl, 1-hydroxyC₃₋₁₈heterocycloalkyl, or 1-C₁₋₆alkoxyC₃₋₁₈heterocycloalkyl, and

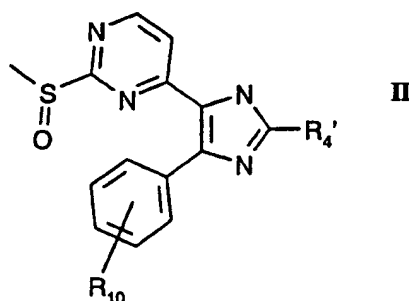
X' is -NH-Y'-, -O- or -S-, where Y' is -CH₂-, -CH₂-CH₂-, -CH(CH₃)- or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

4. A compound according to claim 1 as described in any one of Examples 1 to 28.
5. A method of inhibiting production of soluble TNF, especially TNF α , or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of a compound according to claim 1.
6. A compound according to claim 1 for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
7. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

8. Use of a compound according to claim 1 in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.
9. A process for the preparation of a compound of formula I''



wherein R_4' , R_5' and R_{10} are as defined in claim 3 and X'' is -NH- or -O-, which comprises reacting the corresponding precursor compound of formula II



wherein R_4' and R_{10} are as defined in claim 3, with the corresponding $R_5'-NH_2$ or $R_5'-OH$ derivative.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/08358

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/04 C07D401/14 A61K31/505 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 97 25045 A (SMITHKLINE BEECHAM CORP ;ADAMS JERRY L (US); BOEHM JEFFREY C (US);) 17 July 1997 (1997-07-17) claims 1,14 ---	1-9
X	WO 96 40143 A (SMITHKLINE BEECHAM CORP ;ADAMS JERRY LEROY (US); GALLAGHER TIMOTHY) 19 December 1996 (1996-12-19) claims 1,10 --- -/-	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 March 2000

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INTERNATIONAL SEARCH REPORT

Int. l. Application No

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